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RESEARCH ARTICLE

Efficacy of immunotherapy and prognosis in anti-LGI1 encephalitis patients: A meta-analysis

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ABSTRACT

Objective: To assess the efficacy and safety of immunotherapy for LGI1 antibody encephalitis, and consider the predictors of poor outcomes following immunotherapy. **Methods**: We searched PubMed and Embase for articles reporting the immunotherapy data of anti-LGI1 encephalitis patients. The proportions of patients with poor outcomes (modified Rankin Scale [mRS] score > 2) at 3 months, 12 months, and the last follow-up, as well as the odds ratio [OR] of predictors were pooled. **Results**: The review included 162 articles with 1066 patients. The proportion of patients with poor functional outcomes was 21% at 3 months, 14% at 12 months, and 14% at the last follow-up after receiving immunotherapy. The proportion of patients with reported relapse was 16.6%. The mean duration from onset to the first relapse was 15.6 months. Predictors significantly associated with poor outcomes were age (increase of 1 year), the presence of cognitive impairment, and CSF LGI1 antibody positive. We did not find a statistically significant association between the worst mRS score in the acute phase, the presence of faciobrachial dystonic seizures (FBDS), days from symptom onset to immunotherapy, second-line treatment, maintenance immunotherapy, or follow-up time and outcomes. **Interpretation**: Although most patients respond to immunotherapy, a minority of patients still have poor outcomes. Advanced age, cognitive impairment, and CSF LGI1 antibody positive are associated with an increased risk of poor outcomes. However, due to the insufficiency of the data, these conclusions need to be interpreted with caution.

Introduction

Anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis is a group of severe antibody-mediated brain diseases for which affected patients present with mental symptoms, memory loss, faciobrachial dystonic seizures (FBDS), and hyponatremia, etc.[1,2] Although the immunotherapy response rate in patients with anti-LGI1 encephalitis varies between 67% and 92%,[2–8] symptomatic seizures, neuropsychiatric symptoms, cognitive impairment, and other sequelae were often remain.[9–11] In addition, the recurrence rate of this disease can reach 14%–35%,[12,13] which imposes enormous physical, psychological, social, and economic burdens on individuals and their families.[14,15]

Previous studies have reported that the course of recurrence and delayed treatment are closely related to adverse outcomes and sequelae.[7,16,17] Therefore, early identification and timely management of patients with risk factors related to poor outcomes are important. The relationships among age,[6,17–19] cognitive impairment,[6,17,20,21] FBDS frequency,[6,17,21] cerebrospinal fluid (CSF) LGI1 antibody (Ab),[6,21,22] and poor outcome have also been investigated. However, these findings are inconsistent. For instance, studies by Muñiz-Castrillo et al. showed that older age increased the risk of poor outcome,[6,19,23] but Thompson et al. did not find an association between age and poor outcome.[17,18] In addition, the findings of Thompson's study indicated that

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the risk of poor outcomes increased fivefold in patients with cognitive impairment,[17] but the findings of Dong et al.'s studies suggested that cognitive impairment had no effect on poor outcome.[6,20,21]

Given the current controversial results, we conducted a systematic review and meta-analysis to clarify the effects of various factors on disease outcome. Furthermore, although immunotherapy is widely used, its strategies are mostly formulated by experienced doctors, especially for second-line treatment and maintenance treatment. To date, there is no clear guide for optimal management. Thus, in order to provide higher quality evidence to help develop the best treatment strategy, we summarized the current use and safety of immunotherapy for anti-LGI1 encephalitis patients and analyzed the functional outcome and recurrence rate of patients after immunotherapy, so as to help clinicians develop treatment plans.

Methods

Search strategy

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement. Two reviewers independently searched PubMed and Embase for relevant articles published in English with no time restrictions. The following search keys were used: "Anti-leucine-rich glioma inactivated 1 encephalitis" OR "Anti-LGI1 encephalitis" OR "leucine-rich glioma-inactivated 1 antibody encephalitis" OR "LGI1 antibody encephalitis".

Inclusion and exclusion criteria

Articles were included in the systematic review according to the following criteria: (1) articles that reported data from patients who met the criteria for definite LGI1 encephalitis according to a recent consensus statement[24,25]; and (2) articles that reported immunotherapy data from anti-LGI1 encephalitis patients were reported. Articles were excluded based on the following exclusion criteria: (1) articles not published in English; (2) animal studies, review articles, letters; and (3) articles reporting data from patients that were already reported in previous reports (duplicate cases). Among the 162 articles included in the systematic review, the articles with fewer than three patients were excluded. As a result, the remaining 23 articles were included in the meta-analysis. With the 23 studies included in the meta-analysis, we conducted meta-analyses for functional outcomes at 3 months, 12 months, and the last follow-up.

Data extraction and quality assessment

Two reviewers independently screened article titles and abstracts, and articles that met inclusion criteria were obtained for full-text assessment. Information extracted included: author, year of publication, participant characteristics, treatment regimens, outcome measures, and recorded adverse effects. Two authors respectively extracted and cross-checked the data, and any disagreement was resolved by discussion until consensus was reached or by consulting a third author. Missing data were handled by contacting study investigators to obtain unreported data or additional details. The quality assessment of observational studies was evaluated according to the Newcastle–Ottawa Scale (NOS)[26] (Table S3). Discrepancies were resolved through negotiation.

Study definitions

Abnormal electroencephalography (EEG) findings were defined as focal or diffuse slow, disorganized activity, epileptic activity, extreme delta brush, seizures or status epilepticus recorded. Abnormal cerebrospinal fluid (CSF) findings were defined as pleocytosis >4 cells/μL, hyperproteinorrachia (total CSF protein level > 45 mg/dL without pleocytosis), or oligoclonal bands positive. Abnormal brain magnetic resonance imaging (MRI) findings were defined as an abnormal signal in the unilateral or bilateral medial temporal lobe, or in the basal ganglia. Poor functional outcome was defined as a final modified Rankin Scale (mRS) score of 3–5 assigned after 12 months from disease onset (inferring a mRS score of 3–5 at 12 months) or a mRS score of 6 (death from anti-LGI1 encephalitis) at any time. Relapse was defined as new onset or a worsening of symptoms after an initial improvement or stabilization for at least 2 months.[27]

First-line immunotherapy included corticosteroids, intravenous immunoglobulin (IVIG), and therapeutic apheresis (TA). Second-line immunotherapy included rituximab, cyclophosphamide, ocrelizumab, intravenous or intrathecal methotrexate, tacrolimus, tocilizumab, bortezomib, and steroid-sparing agents. Long-term immunotherapy (≥6 months) included mycophenolate mofetil, azathioprine, IVIG, methotrexate, corticosteroids, and rituximab redosing.

Statistical analysis

The outcomes were, (1) the proportion of patients with poor functional outcome at 3 months and 12 months from disease onset and at the last follow-up and (2) the ORs of potential risk factors for poor functional outcomes of anti-LGI1 encephalitis. The heterogeneity across

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each effect size was evaluated with the I^2 statistics. $I^2 < 25\%$ was recognized as homogeneity, $25\% \leq I^2 < 50\%$ as low heterogeneity, $50\% \leq I^2 < 75\%$ as moderate heterogeneity, and $I^2 > 75\%$ as high heterogeneity.[28] When I^2 was <50%, a fixed-effect model was used for meta-analysis. When I^2 was >50%, a random-effect model was used. Funnel plots were constructed to visualize the publication bias. Sensitivity analysis was performed by eliminating one study at a time to evaluate the stability of the results and explain the possible source of heterogeneity. A subanalysis was conducted focusing on the cognitive performance of anti-LGI1 encephalitis patients at the last follow-up after immunotherapy, as cognitive performance is an important measure for evaluating patient outcomes. For the risk factors that were reported with odds ratios (ORs) in the original studies, we conducted a meta-analysis directly using their OR values. These factors included the mean age (increase of 1 year), the proportion of patients with CSF antibody positivity, cognitive impairment, and FBDS. For covariates that were not reported with odds ratios (ORs) in the original studies, a meta-regression was performed to assess the influence of the covariates on the proportion of patients with poor functional outcome at the last follow-up. These covariates included the worst mRS score in the acute phase, days from symptom onset to immunotherapy, the proportion of patients receiving second-line treatment or maintenance immunotherapy, and follow-up time. The meta-regression was performed using aggregate summary statistics from the included studies, and the model used for meta-regression was a linear model. Separate models were used to examine each covariate. A p-value < 0.05 was considered statistically significant. The missing data were addressed by complete case analysis, with only studies having the covariate and outcome of interest being included in the model. The meta-analysis was performed using R statistical software (version 4.1.2).

Results

Overview of descriptive data

The database searches yielded 1538 articles. After removing duplicates, our searches returned 1027 articles. A total of 162 articles that met our inclusion criteria were included in the systematic review (Fig. 1), including a total of 1066 individuals (416 females and 648 males [sex was not specified in 2 patients]). The mean (range) age at onset was 60 (1–92) years (data available for 1062 patients). The median (range) number of days from symptom onset to hospitalization was 75 (0–2920) (data available for 96 patients). The worst mRS score in the acute phase was reported in 541 of 1066 patients (mean: 3, range: 0–5). Eighteen of 227 (7.9%) patients required ICU admission. A total of 1006 of 1066 (94.4%) patients received first-line immunotherapy (Table S1). Among 1066 patients, 848 (84.3%) received corticosteroids, 448 (44.5%) received IVIG, and 98 (9.7%) received TA. A total of 245 of 724 (33.8%) patients received second-line immunotherapy, and 338 of 782 (43.2%) patients received maintenance immunotherapy. The mean (range) number of days from symptom onset to immunotherapy was 100.3 (5–330) (data available for 206 patients). Overall, the mean follow-up duration was 29.7 months, ranging from 1 to 184 months (data available for 720 patients). The mean (range) mRS score at last follow-up was 1 (0–6) (data available for 669 patients) (Tables 1 and 2).

Efficacy and adverse events

The proportion of patients with poor functional outcome (mRS score >2) was 21% (95% CI: 9%–33%) at 3 months (data available for 45 patients from four studies) (Fig. 2), 14% (95% CI: 10%–18%) at 12 months (data available for 250 patients from 5 studies) (Fig. 3), and 14% (95% CI: 11%–18%) at the last follow-up (data available for 421 patients from 10 studies) (Fig. 4) after receiving immunotherapy. The proportion of patients with reported relapse was 16.6% (122 of 736). The mean duration from onset to the first relapse was 15.6 months (data available for 279 patients). Post-relapse treatments were reported for 37 patients, 29 of whom received immunotherapy again while the other eight did not. The condition improved in 14 of 18 patients. Only three studies recorded risk factors related to recurrence: advancing age, a lower Barthel index at discharge, and sleep disorders in the acute phase.[13,22,23]

A total of eight articles reported on the cognitive performance of patients at the last follow-up after receiving immunotherapy. However, different studies had variations in the choice of cognitive assessment scales. Addenbrooke's Cognitive Examination (ACE),[29] the Cognitive Performance Score (CPS),[30] the Cambridge Neuropsychological Test Automated Battery (CNPAB),[12] the Rey Auditory Verbal Learning Test (RAVLT) and Rey-Osterrieth Complex Figure Test (ROCF),[7] and the Mini-Mental State Examination (MMSE)[9,17,31,32] were used in one, one, one, and four studies, respectively. Therefore, the four studies in which the MMSE was used as the cognitive assessment scale were included in the subanalysis. The proportion of patients with cognitive impairment at last follow-up was 49% (95% CI: 23%–75%) (data available for 168 patients from four studies) (Fig. S4).

Adverse effects were recorded in 68 of 225 (30%) patients treated with immunotherapy. Specifically, 24 of 68 (35.3%) adverse effects were caused by steroids

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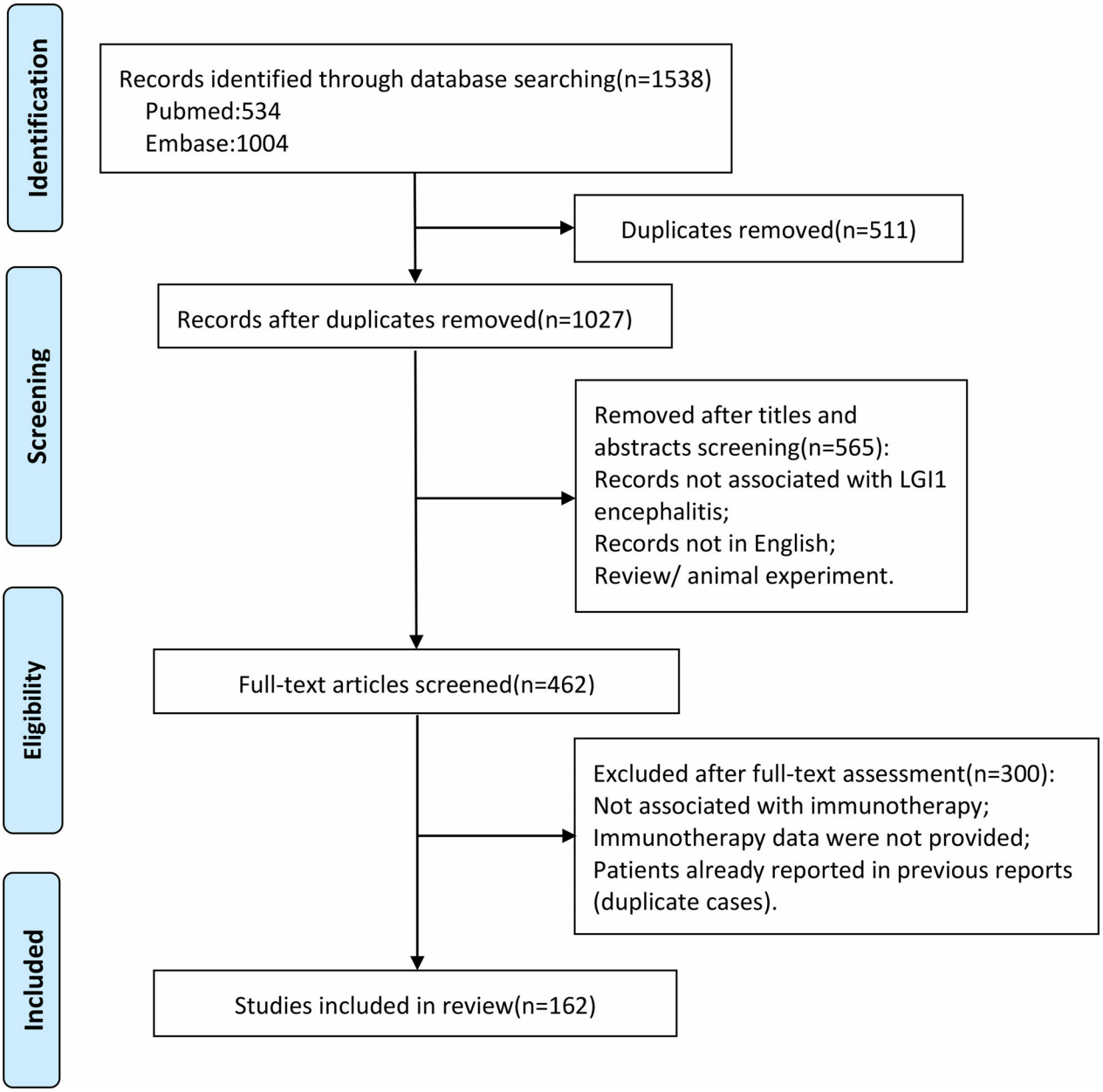

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. LGI1, leucine-rich glioma-inactivated 1.

(recurrent unsightly facial mycosis and marked diabetes mellitus were noted in one patient; insomnia, mood disturbances, and weight gain were noted in 23 patients). Five of 68 (7.4%) were caused by IVIG (including headache, rash, and fatigue). Seven of 68 (10.3%) adverse effects were caused by TA, including the colonization of the catheter tip with coagulase-negative staphylococcus requiring antibiotic therapy (n = 1) and upper respiratory infection (n = 1). Five deaths were attributed to complications from TA [acute respiratory distress syndrome (n = 2), sepsis (n = 2), and pulmonary embolism (n = 1)]. Among 32 of 68 patients, mood (n = 21) and the musculoskeletal system (n = 11, myopathy, tendon rupture, and osteoporosis) were affected by immunotherapy (it was not mentioned which immunotherapy was responsible).

Predictive factors of poor functional outcomes at the last follow-up

Treatment factors associated with functional outcome were assessed through meta-regression. The covariates

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Table 1. Descriptive data on immunotherapy at first event and long-term outcome.

Treatment	No./total No.(%) Total literature cohort (N = 1066)
First-line immunotherapy	1006/1066 (94.4)
Corticosteroids	848/1006 (84.3)
IVIG	448/1006 (44.5)
TA	98/1006 (9.7)
First-line immunotherapy combination	
Corticosteroids + IVIG	270/729 (37.0)
Corticosteroids + IVIG + TA	33/729 (4.5)
Corticosteroids only	226/729 (31.0)
Corticosteroids + TA	48/729 (6.6)
IVIG only	84/729 (11.5)
IVIG + TA	4/729 (0.5)
TA only	9/729 (1.2)
No first-line immunotherapy	55/729 (7.5)
Second-line immunotherapy	245/724 (33.8)
Rituximab	114/679 (16.8)
Cyclophosphamide	64/679 (9.4)
Other[a]	7/679 (1.0)
No second-line immunotherapy	494/679 (72.8)
Maintenance immunotherapy ≥ 6 mo	338/782 (43.2)
Mycophenolate mofetil	71/746 (9.5)
Azathioprine	43/746 (5.8)
IVIG	9/746 (1.2)
Methotrexate	19/746 (2.5)
Corticosteroids	202/746 (27.1)
Rituximab redosing	1/746 (0.1)
Days from symptom onset to immunotherapy	Mean 100.3, range 5–330 (d.a.:206/1066)
Outcome	
Length of follow-up, mo	
Patients	720/1066 (67.5)
Mean	29.7
Range	1–184
Proportion with reported relapse	122/736 (16.6)
The mean duration from onset to the first relapse (mon)	15.6 (d.a.:279/1066)
mRS score at last follow-up	
Patients	669/1066 (65.6)
Mean	1
Range	0–6
Poor functional outcome at 12 mo	44/297 (14.8)
Poor functional outcome at last follow-up	69/494 (14.0)
Motality rate	21/306 (6.9)

IVIG, intravenous immunoglobulin; TA, therapeutic apheresis.
[a]Other second-line immunotherapy drugs include ocrelizumab, intravenous or intrathecal methotrexate, tacrolimus, torcilizumab, steroid-sparing agents, bortezomib.

Table 2. First-line immunotherapy at first event of LGI1 encephalitis.

Data on first-line immunotherapy at first event of anti-LGI1 encephalitis in the total literature cohort (N = 1066)	
First-line immunotherapy	1006/1066 (94.4%)
Corticosteroids	848/1006 (84.3%)
Type of corticosteroids (regardless of the route of administration)[a]	
Methylprednisolone	285/330(86.4%)
Prednisone	223/330 (67.6%)
Other (dexamethasone, ACTH, hydrocortisone, bethamethasone)	20/330 (6.1%)
Route of administration (regardless of type of corticosteroid)[a]	
Intravenous	466/498 (93.5%)
Oral	246/498 (49.4%)
Intravenous immunoglobulin	448/1006 (44.5%)
Therapeutic apheresis	98/1006 (9.7%)
Type of apheresis[a]	
Plasmapheresis	94/98 (95.9%)
Immune adsorption	4/98 (4.1%)
Total number of first-line immunotherapies	
0	31/692 (4.5%)
1	308/692 (44.5%)
2	322/692 (46.5%)
3	31/692 (4.5%)

ACTH, adrenocorticotropic hormone; d.a., available data; n.a., not available.
[a]Denominators refer to the total number of patients who received the treatment, with available data (i.e., total number of patients who received corticosteroids, with available data on corticosteroid type).

included the worst mRS score in the acute phase, days from symptom onset to immunotherapy, the proportion of patients receiving second-line treatment or maintenance immunotherapy, and follow-up time. The results showed no significant correlation between the outcome and the following variables: days from symptom onset to immunotherapy (p = 0.113, 95% CI: −0.0003 to 0.003) (data available for 121 patients from four studies), treatment with second-line (p = 0.540, 95% CI: −0.127 to 0.243) (data available for 299 patients from six studies), and maintenance immunotherapy (p = 0.872, 95% CI: −0.239 to 0.282) (data available for 265 patients from four studies). Patient characteristics associated with increased odds of poor outcome were the mean age (increase of 1 year) (OR: 1.03, 95% CI: 1.01–1.05) (data available for 237 patients from two studies), the presence of cognitive impairment (OR: 2.61, 95% CI: 1.15–5.93) (data available for 285 patients from four studies), and CSF LGI1 antibody positive (OR: 1.89, 95% CI: 1.08–3.31) (data available for 242 patients from three studies). However, the presence of FBDS (OR: 1.00, 95% CI: 1.00–1.01) (data available for 278 patients from four studies), the worst mRS score in the acute phase (p = 0.449, 95% CI: −0.055 to 0.125) (data available for 236 patients from seven studies), and follow-up time (p = 0.878, 95% CI: −0.004 to 0.003) (data available for 334 patients from eight studies) were not associated with poor outcome (Fig. 5). Details of factors not included in the meta-analysis are shown in Table S4.

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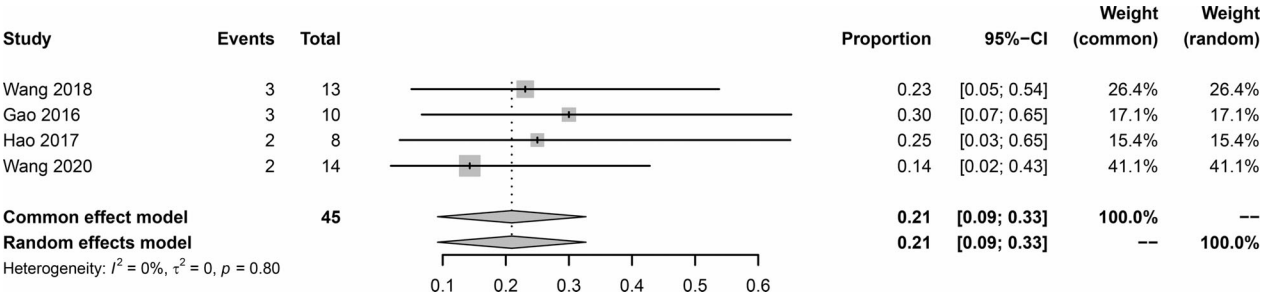

Figure 2. Forest plot showing the proportion of poor functional outcome at 3 months. CI, confidence interval.

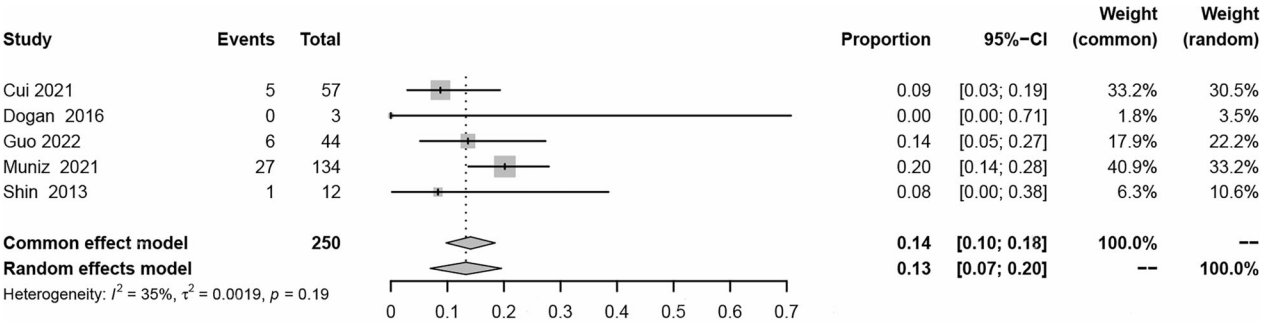

Figure 3. Forest plot showing the proportion of poor functional outcome at 12 months. CI, confidence interval.

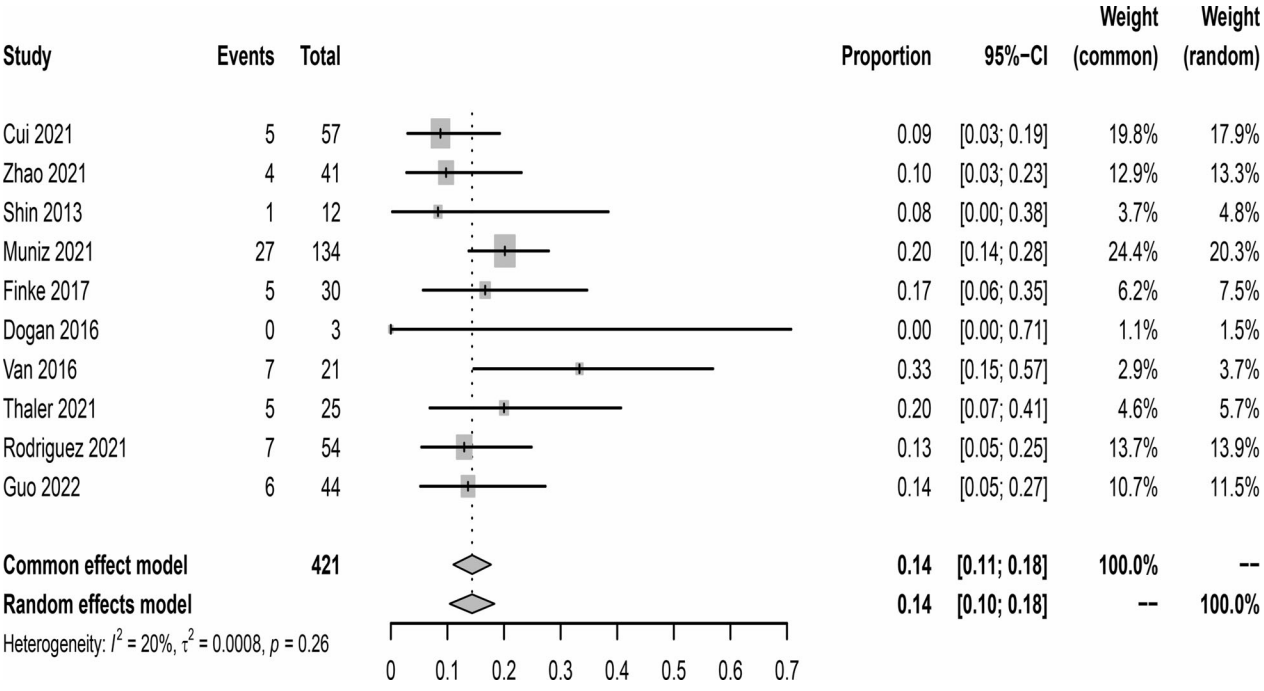

Figure 4. Forest plot showing the proportion of poor functional outcome at last follow-up. CI, confidence interval.

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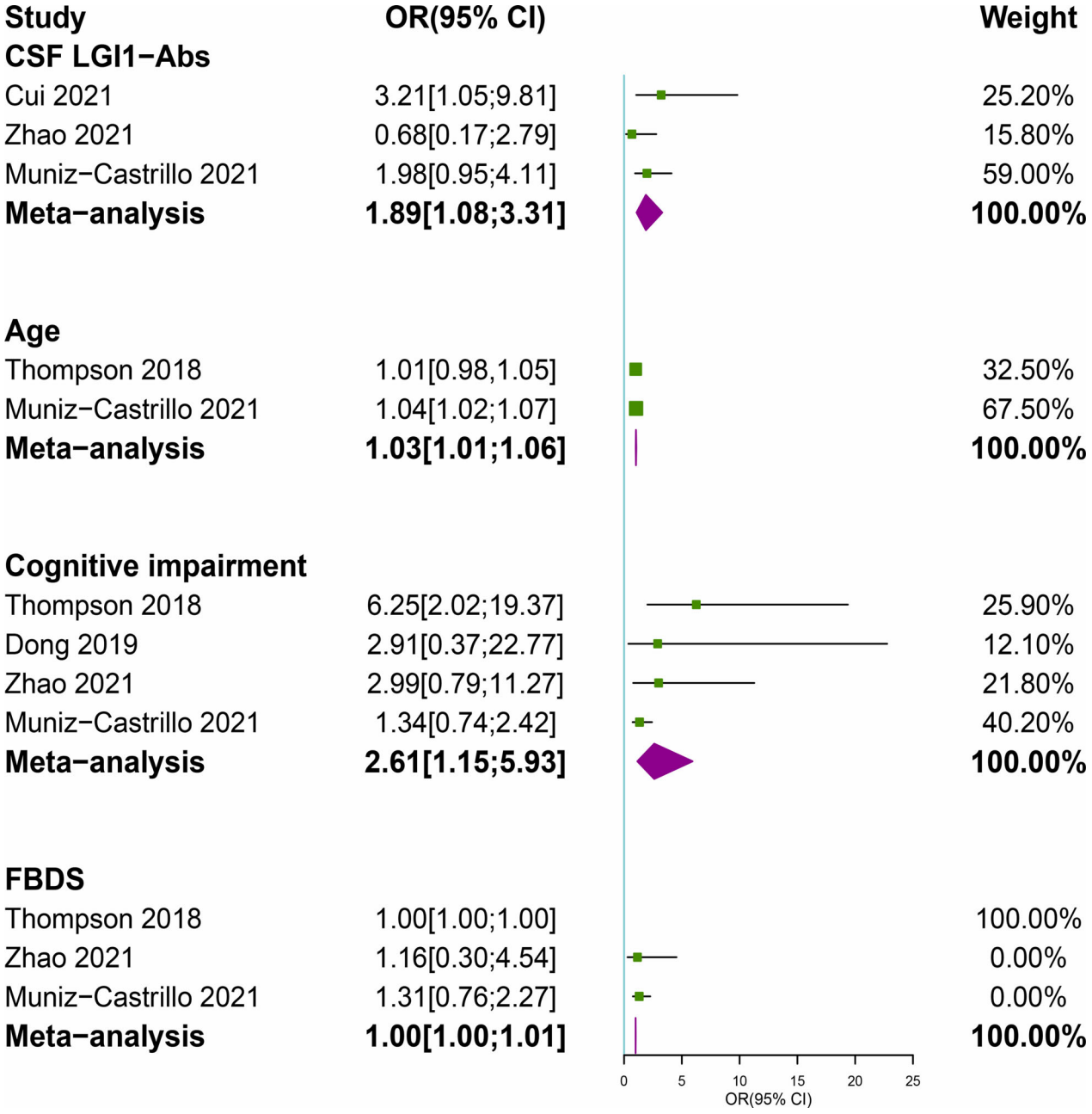

Figure 5. Forest plot (from random-effects analysis) of the associations between CSF LGI1-Ab, age, cognitive impairment, FBDS and poor functional outcome of anti-LGI1 encephalitis patients. Ab, antibody; CI, confidence interval; CSF, cerebrospinal fluid; FBDS: faciobrachial dystonic seizure; LGI1, leucine-rich glioma-inactivated 1; OR, odds ratios.

Quality assessment, sensitivity analysis, and publication bias

According to the NOS, the mean quality of the included studies was 7.94 ± 0.25 and ranged from seven to eight. Scores for each individual article are available in Table S3. We performed a planned sensitivity analysis (Table S5) by eliminating one study at a time, and the outcome was stable. The presence of publication bias was detected by an observed asymmetry in the funnel plots of at 3 months and 12 months. Visual inspection of the funnel plot from the last follow-up did not show a potential publication bias. (Figs. S1–S3). A trim and fill analysis was performed with two imputed studies resulting in an

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adjusted overall effect size of 0.18, 95% CI (0.08–0.28), at 3 months (observed: 0.21, 95% CI [0.09–0.33]) and 0.15, 95% CI (0.09–0.20), at 12 months (observed: 0.14, 95% CI [0.10–0.18]).

Discussion

To our knowledge, this is the first systematic review and meta-analysis of immunotherapy efficacy and risk factors associated with poor outcome in anti-LGI1 encephalitis patients, which provided several important findings with practical implications. The proportion of patients with poor functional outcome (mRS score > 2) was 21% at 3 months, 14% at 12 months, and 14% at the last follow-up. The proportion with reported relapse was 16.6%. The mean duration from onset to the first relapse was 15.6 months Three predictors that were associated with poor outcome were identified: age (increase of 1 year), the presence of cognitive impairment, and CSF LGI1 antibody positive. We did not find an association between the worst mRS score in the acute phase, the presence of FBDS, days from symptom onset to immunotherapy, second-line treatment, maintenance immunotherapy, or follow-up time, and outcome for the cohort overall.

In this meta-analysis, the detailed clinical information, functional outcomes, and predictive factors for poor outcomes of patients with anti-LGI1 encephalitis were evaluated. As the two most common subtypes of autoimmune encephalitis (AE) are AE with antibodies against NMDA receptors (NMDAR) and AE with antibodies against leucine-rich glioma inactivated protein-1 (LGI1),[33] we previously compared the differences in clinical information between patients with these two types of encephalitis. In this study, anti-LGI1 encephalitis predominantly affected middle-aged and elderly individuals, with a slightly higher proportion of males than females, whereas NMDAR encephalitis primarily occurred in young and middle-aged females.[27,34] Clinical seizures were observed in 82.8% of anti-LGI1 encephalitis patients, but only 6.2% experienced status epilepticus. Among the 914 patients, 49.8% were found to have faciobrachial dystonic seizures (FBDS), which is considered a unique clinical feature of anti-LGI1 encephalitis.[35] Among the 849 patients, 53.5% experienced hyponatremia, which is often attributed to the syndrome of inappropriate antidiuretic hormone secretion and may be related to LGI1 expression in the hypothalamus and kidneys.[2] Among the 227 patients, only 7.9% required ICU admission, indicating a lower proportion of severe cases compared to anti-NMDAR encephalitis.[36] Furthermore, patients with anti-LGI1 encephalitis had lower rates of language impairment, movement disorders, autonomic dysfunction, impaired consciousness, and sleep disorders than those with anti-NMDAR encephalitis.[36] The sensitivity of LGI1 receptor antibody testing is higher in serum than in CSF, while the sensitivity of NMDAE antibody testing is higher in CSF.[37] The proportion of patients with poor functional outcome (mRS score > 2) was 14% (95% CI: 10%–18%) at 12 months, and the proportion of patients with reported relapse was 16.6%. Compared with a meta-analysis conducted in 2021, we found that patients with anti-LGI1 encephalitis were more likely to achieve a good functional outcome at 12 months but were more prone to recurrence than patients with NMDAR antibody encephalitis.[36]

In the previous studies, it has been reported that compared with antiepileptic drugs, immunotherapy has higher efficacy and fewer adverse reactions, and may prevent brain atrophy and cognitive impairment.[1,17,31,38–40] In this meta-analysis, the proportion of patients with poor functional outcomes was 21% at 3 months, 14% at 12 months, and 14% at the last follow-up after receiving immunotherapy. Although most patients respond to immunotherapy, a minority of patients still have poor outcomes. To explore factors influencing functional outcomes, we performed meta-regression analysis; the results showed that the worst mRS score in the acute phase, days from symptom onset to immunotherapy, second-line treatment, maintenance immunotherapy, and follow-up time did not affect the functional outcome of patients with anti-LGI1 encephalitis. Prior to this study, Halliday et al. conducted a meta-analysis and showed that treatment with second-line immunotherapy was associated with higher final mRS scores in subgroups with anti-LGI1 encephalitis, which was inconsistent with our finding.[41] The discrepancy between Halliday's study findings and our research findings may be related to the difference that Halliday's study employed IPD meta-analysis, while we utilized summary statistic meta-regression. The difference in statistical methods could be a contributing factor to the inconsistent results. Furthermore, the studies included in Halliday's meta-analysis tended to be smaller and focused on early-stage research, whereas the studies included in our meta-regression had larger sample sizes and were more recent. The differences in the included studies may be one of the reasons for the discrepancies in the results. Moreover, a large study reported that second-line treatment is effective for autoimmune encephalitis regardless of antibody status.[42] Future longitudinal studies in population-based cohorts will be necessary to further evaluate the efficacy of second-line treatment for anti-LGI1 encephalitis. There is currently no study of the efficacy of maintenance immunotherapy. Regarding first-line immunotherapy, we summarized the data on the current combinations of various first-line immunotherapies, among which corticosteroids alone (37% of cases) and

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corticosteroids plus IVIG (31% of cases) were the most common first-line treatment strategies. The efficacy of first-line immunotherapy combinations is controversial. According to Rodriguez et al., compared with patients receiving intravenous immunoglobulin, patients receiving single-agent acute corticosteroids were more likely to experience the regression of FBDs and improvements in their mRS scores.[43] However, Shin et al. found that patients treated with steroids and intravenous immunoglobulin had a better prognosis and a lower recurrence rate than patients treated with steroids alone.[5] The discrepancy may be related to the difference in outcome measure selection. In Shin's study, the outcome measure was dichotomized into good and poor outcomes, whereas in Rodriguez 's study, changes in the ordinal mRS score were utilized as the outcome measure. This disparity in outcome measure selection may account for the differing results. Due to the limited data availability, the efficacy differences between different combinations of first-line immunotherapy regimens have not been compared. Studies with more patients and observations are warranted to establish guidelines for the use of first-line immunotherapy in the treatment of anti-LGI1 encephalitis. The subanalysis was conducted focusing on the cognitive performance of anti-LGI1 encephalitis patients at the last follow-up after immunotherapy. However, the number of studies that could be included was limited, and there was substantial heterogeneity among the studies. Such limitations could affect the reliability and interpretability of the subanalysis findings. In future research, it would be valuable to address these limitations by conducting larger and more homogeneous studies specifically examining the cognitive outcomes of anti-LGI1 encephalitis patients. This could involve standardized assessments of cognitive function, consistent follow-up periods, and a larger sample size to improve the statistical power and generalizability of the findings.

Treatment-related adverse effects occurred in 30% of patients. Five deaths were attributed to complications from TA, but most adverse effects were mild. Thus, the serious complications may be specific to TA, and perhaps the other options may be safer. However, a prospective observational case–control study showed that TA resulted in moderate to marked clinical improvement, with a low rate of adverse events.[44] This is different from our findings. Therefore, the risk–benefit ratio of immunotherapy should be carefully evaluated in individual anti-LGI1 patients until its safety can be determined in randomized trails.

Although some articles have explored the risk factors associated with poor outcomes after immunotherapy, the results are contradictory and controversial. According to the available data, we identified three risk factors associated with poor outcome: advanced age, the presence of cognitive impairment, and CSF LGI1 antibody positivity.

The presence of cognitive impairment increased the risk of poor outcome twofold. This irreversible disability in patients with cognitive impairment may be secondary to their higher proportions of LGI1-IgG1 antibodies and associated with hippocampal atrophy with further reduced mediodorsal thalamic and posteromedial cortical volumes. Early initiation of immunotherapy has been proven to be effective in preventing cognitive impairment and improving prognosis.[7,9,17,30] It is worth noting that the results of our meta-regression analysis showed that the number of days from symptom onset to immunotherapy did not affect the functional outcome of patients with anti-LGI1 encephalitis. This contradicts previous research findings, and this contradiction may be attributed to the limited number of studies included in our meta-regression analysis. Therefore, our results should be interpreted with caution. In future research, we will strive to include a larger number of studies to further validate the reliability of the findings. Advanced age was also a risk factor for poor outcome, which was consistent with the results of Li et al.[23] and Muñiz-Castrillo et al.[6] However, the OR and the 95% CI were close to 1 (OR = 1.03, 95% CI = 1.01–1.06). Therefore, caution should be exercised interpreting this finding. Exploring potential differences in treatment and outcomes among different age groups is valuable. However, due to limitations in the original studies included in our analysis, which only reported the mean or median age of patients, we were unable to perform a detailed analysis of treatment types and outcomes based on age groups. Future studies are recommended to consider this aspect when conducting more comprehensive data collection.

The role of CSF antibody positivity in poor prognosis has recently attracted people's attention. Our results showed that CSF antibody positivity increased the risk of adverse outcomes by 89%. It has been reported that patients with detectable LGI1 antibodies in cerebrospinal fluid have more frequently have inflammatory factors in cerebrospinal fluid, hyponatremia, and MRI abnormalities.[6,8,21,22] Thus may indicate that the immune response is stronger and more likely to lead to structural damage and permanent functional defects.[6,8,21,22] In addition, it has been reported that an elevated LGI1-IgG CSF index can predict adverse neurological outcomes.[8] The higher index may indicate the need for more aggressive initial immunotherapy. However, CSF LGI1 antibody negativity does not rule out the production of intrathecal LGI1 autoantibodies. Recently, B cells producing LGI1-Abs have been found in the CSF of patients with CSF LGI1 antibody negativity. This finding indicates that there

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is intrathecal synthesis in these patients, although it may not be detected due to the rapid binding of the antibody to its antigen or a low antibody level.[45] We can consider the existence of LGI1-specific plasmablasts/plasma cells in the CSF as a reason for targeted immunotherapy in patients with refractory cases.[8]

Limitations

This review has some limitations. First, we included observational studies and case reports, which are susceptible to biases, such as the reported patient being worse off or having atypical symptoms than the general population of patients with anti-LGI1 encephalitis, which may be one of the reasons why functional outcomes did not improve. Second, among the studies that met the inclusion criteria, only a few studies reported ORs for factors related to poor outcomes, so the results are not sufficiently comprehensive. To explore more predictors, we performed a meta-regression to assess the influence of covariates on the proportion of patients with poor outcome, but the odds ratios of these predictors are unknown. Another limitation of the meta-regression is that only a small number of studies were included in the meta-regression models, and the missing information on some variables limited the power of our analyses. In this meta-analysis, advanced age, cognitive impairment, and CSF LGI1 antibody positive are associated with an increased risk of poor outcomes. However, due to the insufficiency of the data our conclusions need to be interpreted with caution. Moreover, due to the lack of individual data, we did not compare the efficacy of various first-line immunotherapy regimens. More large-scale and multicenter studies are still needed to guide the formulation of optimal treatment strategies in the future.

Author Contributions

Dong Zhou and Zhen Hong conceived and designed the study. Xueying Kong and Xue Gong selected the articles and extracted and cross-checked the data. Aiqing Li, Yue Liu, and Xingjie Li contributed to the statistical analysis. Xueying Kong, Xue Gong, and Zhen Hong wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1.

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